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Case Report

Riedel's Thyroiditis Presenting as Rapidly Progressive Hypothyroidism: A Case Report and Literature Review

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ABSTRACT

Objective: Riedel's Thyroiditis (RT) is a rare thyroid pathology that presents a challenge for clinicians to diagnose and treat. Its etiology remains unknown, although data suggests an association with Hashimoto thyroiditis, systemic fibrosis, and IgG-4 related systemic disease. Due to its rarity, there is no consensus on treatment. We present a case of progressive hypothyroidism and a rapidly growing thyroid mass prior to diagnosis of RT.

Methods: Laboratory investigations included Thyroid Stimulating Hormone (TSH), free T4, Anti-Thyroid Peroxidase (TPO) and Anti-Thyroglobulin (TG) antibodies, IgG, Parathyroid Hormone (PTH), calcium, and calcitonin levels. Imaging included thyroid ultrasound and chest Computed Tomography (CT). Following fine needle aspiration and core biopsy, immunostaining and flow cytometry were performed.

Results: A 36-year-old woman presented with rapidly progressive neck swelling and progressive hypothyroidism requiring several Levothyroxine dosage increases over a one year span. TSH was 17.40 uU/mL (ref: 0.35-4.94 uU/mL), with a normal T4 while on 150 mcg of levothyroxine. Elevated thyroid autoantibodies (Anti-TPO >700 IU/mL, ref: 0.0-9.0 IU/mL, Anti-TG >2000 IU/mL, ref: 0.0-4.0 IU/mL), with remaining labs normal. Thyroid ultrasound and CT of the chest demonstrated an enlarged, irregular thyroid gland with tracheal deviation and a nodular like area off the posterior aspect of the mid thyroid. She was diagnosed with RT after biopsy and managed medically with Prednisone and Tamoxifen.

Conclusion: Because hypothyroidism is a common diagnosis, especially compared to the rare RT, it is easy for the diagnosis of RT to be delayed until the thyroid mass impinges on adjacent structures. This report highlights how a high index of suspicion is required for diagnosis and the difficulty of treatment due to varying responses and side effects.

Keywords: Riedel's; Thyroiditis; Hypothyroidism; Tamoxifen

Abbreviation: RT: Riedel's Thyroiditis; TPO: Thyroid Peroxidase; TG: Thyroglobulin; IgG: Immunoglobulin G; PTH: Parathyroid; CT: Computed Tomography; TSH: Thyroid Stimulating Hormone; MRI: Magnetic Resonance Imaging; FNA: Fine Needle Aspiration; LCA: Leukocyte Common Antigen; TTF1: Thyroid Transcription Factor 1; HTFV: Fibrous Variant of Hashimoto's Thyroiditis

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INTRODUCTION

Riedel Thyroiditis (RT) is a rare, inflammatory disease of the thyroid gland characterized by replacement of thyroid parenchyma with dense connective tissue. Along with destruction of the follicular cells of the thyroid gland, the dense fibrous tissue can extend beyond the thyroid capsule and involve adjacent structures. This can create a constellation of presenting symptoms, such as hoarseness with recurrent laryngeal nerve involvement, hypocalcemia with parathyroid involvement, and airway compromise due to local tracheal compression. Typically, patients present with a hard, fixed, and gradually growing painless goiter. Compared to other thyroid disorders, Riedel's thyroiditis is very rare and its overall incidence is approximately 1 per 100,000 individuals. It predominantly affects women, with a ratio of 4:1 compared to men, and is commonly diagnosed between the ages of 30-50 [1].

CASE PRESENTATION

A 36-year old woman presented with a two-month history of gradually progressive neck swelling. She developed associated neck pain, decreased range of motion, hoarseness, and dysphagia, without difficulty breathing. One year prior to presentation, she had been diagnosed with hypothyroidism. Her dose of levothyroxine slowly increased over the year and just prior to her neck swelling, her dose was increased from 125 mcg/day to 150 mcg/day when her TSH was found elevated to 13.47. She did not have a family or personal history of thyroid malignancy, however she lived near Chernobyl during her childhood. Of note, the patient was a current every day smoker at time of diagnosis.

On exam, the anterior and lateral neck was hard and enlarged, but nontender to palpation. The range of motion of her neck was diminished. The initial ultrasound of the thyroid demonstrated an asymmetrically enlarged heterogeneous, nodular right thyroid lobe that measured at least 2.4 × 4.0 × 4.7 cm. The ultrasound additionally showed a nodular-like area off the posterior aspect of the mid thyroid measuring 0.9 × 1.1 × 0.8 cm which was unclear if it represented extension of thyroid gland versus a true thyroid nodule or parathyroid nodule. A chest CT with contrast revealed a diffusely enlarged thyroid extending superiorly beyond the imaged field-of-view with mild tracheal displacement. She declined additional MRI or CT scans of the thyroid. Initial laboratory results included TSH of 17.40 uU/mL (ref: 0.35-4.94 uU/mL), and free T4 of 1.06 ng/dL (ref: 0.61-1.82). She was found to have significantly increased thyroid autoantibodies (Anti-TPO >700 IU/mL with ref: 0.0-9.0 IU/mL, Anti-TG >2000 IU/mL with ref: 0.0-4.0 IU/mL). Her serum IgG, PTH, and calcium levels were normal, with calcitonin <2.0 (ref: 0.0-5.1 pg/mL). Of note the lab was unable to stain for IgG4. Normal IgG serum levels does not rule out potential IgG4-mediated disease (Figure 1).

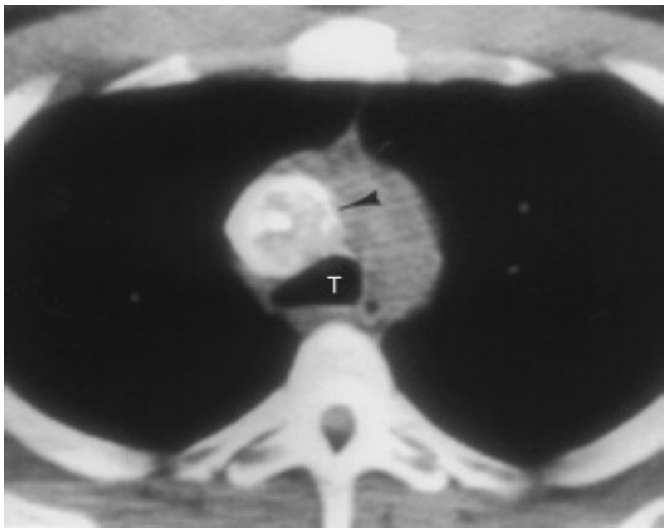

Figure 1: Riedel's thyroiditis presenting as rapidly progressive hypothyroidism.

A subsequent Fine Needle Aspiration (FNA) was non-diagnostic and showed lymphoid tangles with no identifiable follicular epithelium. A core biopsy revealed dense fibrous connective tissue admixed with mature lymphocytes. On immunostaining, the lymphocytes stained positive with antibodies to Leukocyte Common Antigen (LCA) and negative for Thyroid Transcription Factor-1 (TTF1). The FNA, core biopsy and immunostaining were non-diagnostic but raised suspicion for Riedel's thyroiditis or other fibrosis. Flow cytometry was also performed, however, due to low cell yield a limited antibody panel was performed. A population of cells with bright CD45 expression and low side scatter, compatible with lymphocytes were identified. The lymphoid population consisted of approximately 93% T-cells and 7% B-cells. No eosinophils or plasma cells were noted. Among the B-Cells, no evidence of light chain restriction was identified, ruling out lymphoma. Lymphoid tangles and extensive fibrosis with signs of chronic inflammation *via* lymphoid infiltration suggested the diagnosis of Riedel's thyroiditis. Otolaryngology was consulted who determined that there was no airway compromise in the patient.

The patient was then started on prednisone 60 mg daily and levothyroxine 175 mcg daily, which she tolerated for 6 weeks with minor improvement in neck symptoms. Due to adverse side effects, the prednisone dose was titrated down and she was started on 10 mg tamoxifen, which was titrated up to 20 mg. Over the course of 6 months, the patient's compressive symptoms resolved and her follow-up ultrasound showed a significant decrease in thyroid size. Her TSH level normalized with a stable dose of levothyroxine 175 mcg/day. 18 months after her initial presentation, the patient remains asymptomatic with a current dose of tamoxifen 10 mcg/day and is no longer taking prednisone.

DISCUSSION

Riedel Thyroiditis (RT) is an inflammatory process ranging from replacement of a single lobe to the entire thyroid gland. Histologically, the normal thyroid follicles are replaced by a mass

consisting of inflammatory cells, predominantly a mixture of lymphocytes, plasma cells, eosinophils in a dense background of hyalinized connective tissue [2]. Diagnostic criteria for RT include: Extra-thyroidal extension of inflammatory process, presence of occlusive phlebitis, absence of granulomas, lymphoid follicles, or giant cells, and absence of thyroid malignancy [3,4]. The exact etiology of RT is still unclear. A longstanding theory states that RT is one manifestation of Multifocal Fibrosclerosis (MFS) disorder, defined by fibrous lesions occurring at several sites, including the thyroid gland, retroperitoneal fibrosis, and mediastinal fibrosis [5]. It has been documented in case reports since 1960 that over 1/3 of patients diagnosed with RT develop further manifestations of multifocal fibrosis at the same time or later on [6]. There have also been cases involving co-presentation of RT with orbital fibrosis and pancreatic fibrosis [4,6]. Of note, studies have also found an association with tobacco use and the development of MFS [7]. F-18 Fluorodeoxyglucose Positron Emission Tomographic (FDG PET) can be utilized to look for the presence of other areas of fibrotic processes like MFS and evaluate response to treatment [8]. There is also now growing evidence that RT may be a feature of IgG4-related systemic disease [9]. There have been cases described where IgG4+ plasma cells were identified on histology of resected goiters in patients diagnosed with RT [2,9,10]. IgG-4 related systemic disease is an emerging condition defined by IgG4+ plasma cell infiltration of several organs, including sclerosing pancreatitis, RT, and sclerosing cholangitis [11]. The majority of patients with IgG-4 related systemic disease have elevated serum IgG4 concentrations, but up to 30% of patients can have normal serum levels [10]. We were unable to stain for IgG4+ antibodies on our patient's tissue sample. However, her normal IgG serum levels does not rule out potential IgG4-mediated disease.

Due to its rarity, RT is often misdiagnosed or diagnosis is delayed. On presentation, most patients have normal thyroid function, with TSH and T4 within normal limits. Approximately 30% of cases, such as our patient, present with hypothyroidism [10]. Furthermore, the detection of Thyroid Peroxidase (TPO) antibodies occurs in approximately 90% of patients with RT [1]. The hypothyroidism can be due to concomitant Hashimoto's thyroiditis or secondary to the fibrotic destruction of thyroid follicular cells [3]. Our patient is one of few patients described who had rapidly progressive hypothyroidism prior to the actual increase in size of her thyroid gland. In patients with RT who have TPO autoantibodies, it is unclear whether RT develops in a pre-existing Hashimoto's gland or if the destruction from Riedel's thyroiditis leads to antibody formation [12]. There have been rarer case reports involving patients presenting with subclinical hyperthyroidism as well as thyrotoxicosis [9,13].

It is important to differentiate RT from malignancy, which can also present as progressively enlarging thyroid masses. Because the fibrosis can produce a low yield FNA, performing a core biopsy is imperative in anyone with concern for thyroid malignancy. Anaplastic carcinoma typically present in elderly patients with a rapidly enlarging neck mass associated with compression symptoms. It is usually easily differentiated from RT because of its obvious invasive growth, and high atypical cellularity [14].

However, rare paucicellular variants have been described but can still be differentiated from RT *via* presence of infarction, few atypical spindle cells, and immunoreactivity for epithelial markers [14]. The lack of malignant cells in RT also differentiates it from other potential causes of thyroid malignancy, such as thyroid sarcoma and lymphoma [15,16].

It can also be difficult to distinguish RT from a Fibrous Variant of Hashimoto's Thyroiditis (HTFV), especially because thyroid autoantibodies and hypothyroidism can be seen in both conditions. However, HTFV can be distinguished with the presence of granulomatous microabscesses with central necrosis, prominent squamous metaplasia, and fibrosis that does not extend past the thyroid capsule [17].

The overall prognosis of RT is good and after initial presentation, it has been observed that the thyroid mass may stabilize or even regress. However, progressive fibrosis can lead to increasing tracheal compression. Mortality is most commonly due to upper airway compromise [2]. Surgery is limited due to obliteration of tissue planes, leading to potential parathyroid and laryngeal nerve damage with surgical intervention. This is typically limited to debulking surgery and isthmectomy to relieve constrictive pressure [2]. However, thyroidectomy and shaving of the trachea, esophagus and recurrent laryngeal nerve under microscopy has been successful in case reports and could be explored for patients with severe compressive symptoms in the future [18].

Medical therapy is frequently chosen, with several agents available without a consensus in dosing. High dose corticosteroids are typically initiated first, with dose and duration based on tolerability. There have been cases of RT entering remission with solely prednisone, with dosing reports ranging from 15 mg to 100 mg daily [3,12]. However, due to adverse effects, such as with our patient, high dose steroids often need to be tapered down. Although the exact mechanism is unknown, it is thought that Tamoxifen exerts its effect through anti-fibroblast activity via TGF-beta modulation [19]. Treating RT with Tamoxifen has been shown to have good effect, with doses 10-20 mg, given alone or with prednisone [3,13,19]. There have also been reports of successful treatment with Mycophenolate mofetil and Rituximab in cases with refractory symptoms as well [20,21].

CONCLUSION

As described in this review, Riedel's thyroiditis is a rare condition that can progress into a medical emergency and should be suspected in patients presenting with a thyroid mass. Physical neck changes may be preceded by hypothyroidism, possibly rapidly progressive hypothyroidism, as seen in our patient. Clinical awareness of Riedel's symptomatology and laboratory findings should enhance our ability to distinguish and make the diagnosis. Instituting effective treatment that results in improvement of symptoms and reduction in thyroid size can be challenging due to possible poor response or development of side effects.

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